Janssen-Cilag's comments on the Southampton health technology assessment report

Information highlighted in red is commercial in confidence

Overall comment	To participate fully in the consultation, we would like to request that NICE reconsider releasing the economic model to all consultees. If Janssen-Cilag's commercial in confidence data is considered an obstruction then we would like to discuss how this might be addressed to allow a complete consultation process to take place.
Page 11 and 205	Although the aim of the qualitative analysis was to carry out a systematic review of the clinical effectiveness, we feel there have been inconsistencies in the approach the RCTs assessing thalidomide in combination with MP or CDa have been appraised. The abstracts of the RCTs comparing MPT to MP (NMSG group - Gulbrandsen et al; HOVON group - Wijerman et al) groups were excluded due to the limited reporting of methodological details and outcomes data available in the abstract. This approach is inconsistent with the approach taken with the Myeloma IX study, also available in abstract form and for which the assessment group contacted the investigators in order to obtain more information (e.g. study protocol, results) Our submission supplemented the abstracts by Gulbrandsen and Wijermans by the survival curves for OS and PFS presented at conferences allowing meta-analysis of all the relevant endpoints. (Appendix 7 of our submission)
Page 11	It is unclear why the RCTs including a maintenance phase like the one by Palumbo and Wijermans did not meet the inclusion criteria of the systematic review. Even with the maintenance treatment the duration of treatment with Thalidomide was 8 months in the Palumbo RCT which is shorter than the duration of treatment observed in the RCTs by Facon (11 months) and Hulin (13.5months).
Page 12	There is a misinterpretation of our data by the assessment group with regard to the average number of vials being used in the VISTA trial (n=31.5). The lower number of vials used is the result of doses being withheld, dose reduction and discontinuation rather than vial sharing as stated on page 12. Details on the dose modification can be found in page 126 of the J&J Velcade CSR 1 This has led the assessment group to use a number of vials as per protocol (n=52) which does not reflect the actual number of vials being used in the trial. Furthermore the efficacy observed in the VISTA trial is based on the average number of vials being used not on the number of vials as per protocol.
Page 14	'A MTC was not carried out because of doubts about the validity of doing so due to potential differences in participant

	characteristics, delivery of MP treatment and differences in length of follow-up.' As indicated in our submission we have assessed the heterogeneity between efficacy estimates in the MPT studies and it did not appear to be explained by differences in important trial characteristics such as age, daily dose of thalidomide or the use of maintenance thalidomide treatment. Furthermore both Kumar et al. and Kapoor et al have undertaken a meta-analysis of the MPT RCTs, therefore implicitly considering that the key trials' characteristics are homogeneous enough to allow pooling of the data. • Kumar et al. Thalidomide Versus Bortezomib-Based Regimens for Relapsed Myeloma: Meta-Analysis and Indirect Meta-Analysis. ASH 2008 (abstract 2362). *Although the title is in relapsed myeloma, the abstract is on front line treatment.* • Kapoor et al 2009. Melphalan and Prednisone (MP) Versus Melphalan, Prednisone and Thalidomide (MPT) as Initial Therapy for Previously Untreated Elderly and/or Transplant Ineligible Patients with Multiple Myeloma: A Meta-Analysis of Randomized Controlled Trials ASH 2009 (Abstract 615) We feel that a meta-analysis of the five RCTs comparing MPT to MP needs to be undertaken to inform the decision-making.
Page 48	Table 5 states that it is unclear how missing data were accounted for in the VISTA trial. However our submission contains a paragraph on page 29 on how missing data were imputed. Detailed explanation is also included in the clinical study report provided in appendix of our submission. We would like the table 5 to be revised accordingly.
Page 50	Table 6. It is incorrect to state that the HR for overall survival and p-value after a median follow-up of 36.7months have not been reported as the information is included in the abstract by Mateos (reference 60): HR=0.653, p= 0.0008
Page 59-60	The median progression free survival (PFS) stated on page 59 and in the Table 10 page 60 is incorrect. The PFS values should be as follows: [redacted] (J&J Velcade CSR1 page 145)
Page 61	The reference in the Table 11 should be number 61.
Page 114	It is assumed that each patient in the VMP arm receive 1 vial of bortezomib per administration. This is a dose as per protocol. As the efficacy observed in the VISTA trial is based on the actual average number of vials being used not on the number of vials as per protocol we request a revision of the model to include the average number of vials used in the VISTA RCT (n=31.5).

Page 123	Utility estimates for the treatment and post-treatment periods are specified however it is unclear in the report what the utility estimate is for the post-progression period.
Page 124-125 and 143	The treatment duration of thalidomide is based on clinical expert opinion reflecting clinical practice (10-12months). However the treatment duration should be based on the RCTs (Palumbo, Facon, Hulin) as the efficacy of MPT is obtained for the treatment duration observed in the trial. Similarly the actual average number of vials should be used for Velcade (with a mean treatment duration of 46 weeks for VMP and 39 weeks for MP) instead of using the treatment duration as per protocol (52 vials over 54 weeks)
Page 126	It is assumed that each patient in the VMP arm receive 1 vial of bortezomib per administration. This is a dose as per protocol. As the efficacy observed in the VISTA trial is based on the actual average number of vials being used not on the number of vials as per protocol we request a revision of the model to include the average number of vials used in the VISTA RCT. Using the average number of vial has been misinterpreted as vial sharing while it reflects dose withheld, reduced or treatment discontinuation.
Page 126	The title of table 39 does not reflect the content of the table. It should be replaced by 'Distribution of 2nd line treatments following 1st line treatment'.
Page 132 and 135	'The model results are most sensitive to the HR for OS, cost and dosage of the treatment.' We have highlighted above the key issues around the dose and treatment duration of bortezomib and thalidomide which consequently affect the treatment cost with bortezomib and thalidomide. We also expressed concerns with the exclusion of three RCTs comparing MPT vs. MP (Palumbo, Wijermans and Gulbrandsen); these three trials contain survival outcomes that should be used in the economic model. As shown in the scenario C of the SHTAC model, when these trials are included, MPT no longer dominates VMP. The assessment group also acknowledges that it is difficult to assess the impact of MPT on OS when prescribed according to UK clinical practice. The treatment duration chosen for thalidomide does not reflect the survival outcomes observed across the MPT trials. As the SHTAC model is sensitive to these 3 key parameters we request that these issues be addressed.
Page 140	On page 140 no statement is made with regard the higher complete response rate observed with VMP vs. MP, while a statement is made for MPT vs. MP.
Page 145	Peripheral neuropathy does not necessarily limit the duration of treatment with bortezomib as stated on page 145. As per the SPC the posology of bortezomib needs to be modified according to the severity of peripheral neuropathy. This dose modification means that bortezomib induced peripheral neuropathy can improve, stabilize or completely resolve

	in most patients.